A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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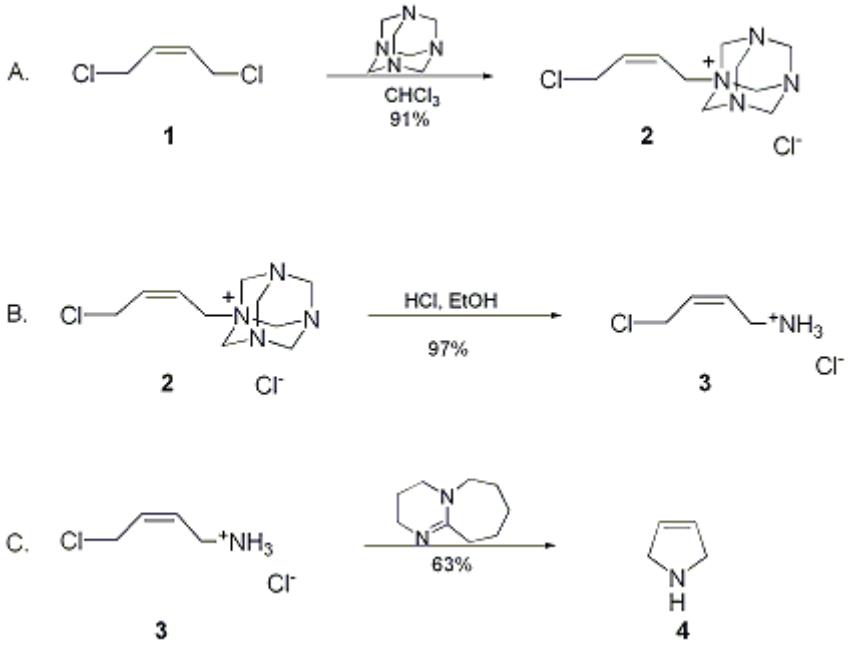
3-PYRROLINE

[1H-Pyrrole, 2,5-dihydro-]



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Checked by Kevin W. Gillman and David J. Hart.

1. Procedure

A. *1-[(Z)-4-Chloro-2-butenyl]-1-azonia-3,5,7-triazatricyclo[3.3.1.1^{3,7}]decane chloride* (**2**). A 1-L, single-necked, round-bottomed flask is charged with 34.4 g (246 mmol) of hexamethylenetetramine and 500 mL of chloroform ($CHCl_3$) (Note 1). cis-1,4-Dichlorobut-2-ene (30.2 g, 242 mmol) is added, the flask is fitted with a reflux condenser (Note 2), and the mixture is heated to reflux with a heating mantle. After 4 hr, the mixture is cooled to room temperature, and filtered through a sintered glass funnel (10–20 μ porosity). The resulting white solid, quaternary salt **2**, is washed with two 100-mL portions of $CHCl_3$, and the filtrate is heated to reflux for an additional 18 hr, cooled, and filtered. The resulting light brown solid **2** is washed twice with 50-mL portions of $CHCl_3$. The combined solids are dried in a desiccator under reduced pressure (1 mm) to afford 58.6 g (91%) of **2** (Note 3).

B. *(Z)-4-Chloro-2-butenylammonium chloride* (**3**). A 1-L, single-necked, round-bottomed flask, equipped for magnetic stirring, is charged with 400 mL of 95% ethanol (EtOH) and 70 mL of concd hydrochloric acid (HCl) is slowly added (slightly exothermic reaction). To the still warm solution is added solid **2** (58.5 g, 221 mmol) in one portion. The reaction initially becomes homogeneous and slightly orange colored, then after 45 min a precipitate begins to form. The reaction mixture is allowed to stir at room temperature for 18 hr, cooled to 0°C, and the precipitate (NH_4Cl) is collected by filtration using a 10–20 μ porosity sintered glass funnel. The collected solid is washed on the funnel twice with 100 mL of cold 95% EtOH. The filtrate is concentrated by rotary evaporation, and the remaining semisolid is taken up in 40 mL of cold 95% EtOH. The resulting precipitate (NH_4Cl) is again collected on the filter and washed with cold 95% EtOH (2 × 20 mL). This procedure (rotary evaporation, solution in 95% EtOH, cooling, filtration) is repeated once more.

The solid remaining upon concentration of the filtrate from the final filtration is dissolved in 80 mL of warm ethyl acetate (EtOAc). Upon cooling, the product crystallizes. Hexane is added (30 mL) and the crystals are collected on a 10–20 μ porosity sintered-glass funnel. The solid is washed with 60 mL of

hexane. The filtrate is concentrated by rotary evaporation to give an additional amount of solid that is recrystallized from a minimum amount of EtOAc and hexane as before. The combined solids are dried in a desiccator under reduced pressure (1 mm) for 2 hr to give 28.1–30.4 g (90–96%) of **3** as a light yellow crystalline solid (Note 4).

C. *3-Pyrroline* (**4**). A 200-mL round-bottomed flask, equipped with a reflux condenser, is charged with 66.4 g (437 mmol) of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) which is cooled to 0°C in an ice bath while **3** (30.3 g, 213 mmol) is added in portions through the top of the condenser. Toward the end of the addition, the resulting slurry becomes orange, gas is evolved, and mixture begins to reflux (the reaction is exothermic). Any remaining salt **3** is added, and, when boiling subsides, a short-path distillation head wrapped in glass wool is put in place (Note 5). A 50-mL receiving flask is totally immersed in a −78°C bath (dry ice-isopropyl alcohol). The orange solid mixture is heated using a heating mantle during which time the solid liquifies and 3-pyrroline (**4**) distills at 85–92°C at atmospheric pressure. (*CAUTION: some foaming occurs initially, but subsides during the reaction)*. Heating is continued until no more 3-pyrroline distills, affording 11.05 g (75%) of 3-pyrroline as a clear oil (Note 6), (Note 7).

2. Notes

1. Hexamethylenetetramine and cis-1,4-dichloro-2-butene (95%) were obtained from Aldrich Chemical Company, Inc., and were not purified before use. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), chloroform, ethyl acetate, and hexane were distilled prior to use.
2. The mixture is left open to air.
3. All physical data for **2** are consistent with that given in reference [2]: mp 160–170°C dec; ^{1}H NMR (D_2O) δ: 3.54 (dd, 2 H, J = 7.9, 0.5), 4.10 (dd, 2 H, J = 8.1, 0.5), 4.43 (d, 3 H, J = 12.9), 4.58 (d, 3 H, J = 12.9), 5.01 (s, 6 H), 5.67 (m, 1 H), 6.23 (complex m, 1 H); ^{13}C NMR (D_2O) δ: 40.5, 55.4, 73.0, 81.1, 119.6, 140.9. The yield of the first crop is 81–82%. The second crop contains a minor impurity as indicated by a doublet at δ 3.79 in the ^{1}H NMR, but is used in the next step.
4. The physical properties of **3** are as follows: mp 117–120°C dec; ^{1}H NMR (D_2O) δ: 3.63 (d, 2 H, J = 7.3), 4.07 (d, 2 H, J = 8.0), 5.58 (m, 1 H), 5.89 (m, 1 H); ^{13}C NMR (D_2O) δ: 38.8, 41.4, 127.5, 134.9. This material is easily stored without any special precautions.
5. The distillation should be carried out under an inert atmosphere.
6. The 3-pyrroline (**4**), prepared as described above, is estimated to be >95% pure. A sample was stored at 0°C in a stoppered, round-bottomed flask for six months with very little oxidation or decomposition; the compound, however, had yellowed. For prolonged storage, a sealed ampoule is recommended. The checkers obtained a somewhat lower yield of **4**using an oil bath at 200°C for the distillation, whereas the submitters employed a heat gun and obtained a 63% yield of **4** (bp 80–85°C).
7. The NMR spectra of 3-pyrroline (**4**) are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.93 (s (broad), 1 H), 3.71 (s, 4 H), 5.84 (s (broad), 2 H); ^{13}C NMR ($CDCl_3$) δ: 53.6, 128.2.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

3-Pyrroline is a desirable starting material for alkylation of heterocycles. 1-(Methoxycarbonyl)-3-pyrroline[3] has been used to prepare 2,5-dialkylated pyrrolines,[4] which resulted in the synthesis of the Pharaoh ant trail pheromone[5] and gephyrotoxin 223.[6] Alkylation of 3-pyrrolines has also led to the synthesis of 12-azaprostaglandins.[7] The submitters have used a formamidine derived from 3-pyrroline to provide access to 2-substituted pyrrolines and pyrrolidines,[8] [9] which has led to the synthesis of the unnatural (+)-anisomycin.[10]

Recently, Brown has shown the feasibility of a one-carbon homologation procedure using a chiral non-racemic boronate derived from the hydroboration of 3-pyrroline.[11] [12] Pyrrole-containing nucleosides have been prepared from the pyrroline nucleoside by photodehydrogenation.[13] [14]

Pure 3-pyrroline has been difficult to obtain. Commercially available 3-pyrroline was at one time supplied in 85% purity, the remaining 15% being pyrrolidine.[15] It is now supplied in only 65% purity. Material of 97% purity is available; however, the cost ($51/g) is excessively high, limiting its use as a starting material.[15,16]

Preparation of N-alkyl-3-pyrrolines has been accomplished by treatment of cis-1,4-dihalo-2-butene with the appropriate amine.[17] [18] [19] However, synthesis of the parent 3-pyrroline by condensation of cis-1,4-dihalo-2-butene with ammonia is a very low-yielding process.[18]

Reduction of pyrrole by zinc/hydrochloric acid (Zn/HCl) leads to various amounts of pyrrolidine as overreduced material.[20] [21] Other preparations of pure 3-pyrroline were found to be difficult or of low yield.[20] [21] [22] [23] [24] [25] Separation of 3-pyrroline from pyrrolidine is difficult, as they differ in boiling points by only 1.5°C.[21] Crystallization of their hydrochloride salts,[21] or urethanes,[26] is possible, but only with significant losses.

A three-step preparation, based on the Delépine reaction,[2] describes the synthesis of this compound in high purity.[27] However, some difficulties were encountered in the hands of the submitters following this procedure.[28] Several modifications have now led to an efficient preparation of 3-pyrroline in high purity, and to a procedure that is readily amenable to large scale synthesis.

References and Notes

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(NH_4Cl)

ethanol,
EtOH (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ethyl acetate,
EtOAc (141-78-6)

chloroform (67-66-3)

hexamethylenetetramine (100-97-0)

Pyrrole (109-97-7)

pyrrolidine (123-75-1)

hexane (110-54-3)

Formamidine

3-Pyrroline,
1H-Pyrrole, 2,5-dihydro-

1,8-diazabicyclo[5.4.0]undec-7-ene,
1,8-diazabicyclo[5.4.0] undec-7-ene (6674-22-2)

cis-1,4-Dichlorobut-2-ene,
cis-1,4-dichloro-2-butene (1476-11-5)

(Z)-4-Chloro-2-butenylammonium chloride (7153-66-4)

1-(Methoxycarbonyl)-3-pyrroline

1-[(Z)-4-Chloro-2-butenyl]-1-azonia-3,5,7-triazatricyclo[3.3.1.$1^{3,7}$]decane chloride (117175-09-4)